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Original article

Noninvasive estimation of pulmonary capillary wedge pressure in patients with mitral regurgitation: A speckle tracking echocardiography study

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ABSTRACT

Background: Echocardiographic parameters to predict pulmonary capillary wedge pressure (PCWP) in mitral regurgitation (MR) are not yet elucidated. We reported that PCWP could be accurately estimated by novel KT index which is defined as $\log_{10}$ [left atrial (LA) emptying function (EF)/LA volume]. We examined the usefulness of the KT index as a predictor of PCWP in primary and secondary MR with sinus rhythm and also MR with atrial fibrillation.
Methods: LA dimension, strain, volume, EF, and E/e' were measured in moderate to severe MR with sinus rhythm ($n = 58$, age: 67 ± 8 years) and MR with atrial fibrillation ($n = 24$, age: 69 ± 11 years) just before catheterization and in normal subjects ($n = 26$, age: 67 ± 11 years) using speckle tracking echocardiography. MR with sinus rhythm was divided into primary MR ($n = 27$) and secondary MR ($n = 31$). The estimated PCWP (ePCWP) was calculated as $10.8 - 12.4 \times$ KT index.
Results: There was a correlation between PCWP and LA dimension, E/e', minimum LA volume index, active LAEF, total LAEF, or LA strain ($r = 0.32$, $r = 0.31$, $r = 0.55$, $r = -0.61$, $r = -0.51$, and $r = -0.50$, respectively, $p < 0.05$). The better correlation was found between PCWP and ePCWP in MR including both primary and secondary MR and also MR with atrial fibrillation ($r = 0.70$, $r = 0.67$, and $r = 0.58$, respectively, $p < 0.01$). Multiple regression analysis revealed that ePCWP was an independent predictor of PCWP in MR. The ePCWP demonstrated good diagnostic accuracy (area under the curve of 0.86) and sensitivity (81%) and specificity (71%) to predict elevated PCWP >15 mmHg using a cut-off of 16 mmHg.
Conclusion: The ePCWP was the reliable echocardiographic parameter to predict PCWP in primary and secondary MR and might also be useful in MR with atrial fibrillation. The ePCWP may have an incremental value in a clinical setting.

Introduction

Echocardiography, especially Doppler echocardiography plays an important role in the diagnosis and treatment of patients with mitral valve regurgitation (MR). It is practical to estimate pulmonary capillary wedge pressure (PCWP) by measuring transmitral inflow velocity by Doppler echocardiography for treatment in those patients, but this method is influenced by factors such as age, heart rate, preload, and afterload [1–3].

It was demonstrated that the ratio of early transmitral inflow velocity to mitral annulus early diastolic tissue Doppler velocity (E/e') correlates with the left ventricular filling pressure (LVFP) measured invasively in patients without MR [4] and E/e' is widely

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used as a non-invasive tool to estimate LVFP. However, existing Doppler and two-dimensional methods including left atrial volume (LAV), mitral inflow pattern, pulmonary vein flow pattern, and E/e' have several limitations when they are applied to the estimation of LVFP in patients with MR [1,5]. There was conflict in the use of E/e' to estimate LV end-diastolic pressure (LVEDP) in MR [1,5]. It was reported that the e' would be increased in patients with MR and preserved LV ejection fraction because of the increased LV stroke volume [1].

In the absence of severe MR, LV pressure at the mitral valve opening (LVFP) correlates closely to mean LA pressure that can be approximated by PCWP [6,7]. The increase in LVFP in patients with heart failure is the primary mechanism responsible for symptoms such as dyspnea. Thus, it is of exceeding importance to estimate LVFP or PCWP in patients with MR to decipher the cause of dyspnea and determine the therapeutic strategy. However, echocardiographic parameters to predict LVFP or PCWP in MR have not been elucidated.

We recently reported that PCWP estimated by the combination of LAV and LA function (ePCWP) using speckle tracking echocardiography (STE) is a strong predictor of PCWP measured by cardiac catheterization [8]. Moreover, LA strain assessed by STE was reported to be a powerful predictor of LVFP in heart failure [9]. Thus, the aim of this study is to examine the most useful and reliable echocardiographic parameter including E/e', ePCWP, and LA strain to predict PCWP in patients with moderate to severe MR dividing MR into primary and secondary using STE.

Materials and methods

Study population and protocol

The study population consisted of 62 consecutive patients with moderate to severe MR and sinus rhythm (SR) and an additional 25 patients with moderate to severe MR and chronic atrial fibrillation (AF) who were referred for clinically indicated cardiac catheterization. We also included 26 age-matched controls for the comparison of echocardiographic parameters. The controls had symptoms such as chest pain and discomfort and underwent electrocardiography and echocardiography. The controls had no abnormal findings on electrocardiography and echocardiography, and did not take any medication. Exclusion criteria in MR patients were the presence of mitral stenosis, moderate to severe aortic valve regurgitation or stenosis, past history of surgery for structural heart disease, and poor echocardiographic recording. Therefore, those who had mitral stenosis ($n = 1$), moderate to severe aortic valve disease ($n = 2$), and poor echocardiographic window ($n = 2$) were excluded. Accordingly, 58 MR patients with SR, 24 MR patients with AF and 26 controls without cardiovascular disease were enrolled in our study. Transthoracic echocardiography including the measurement of LA strain and LAV and LA function using two-dimensional STE (2D-STE) was performed in our echo laboratory by two experienced sonographers just prior to pressure measurements by right heart catheterization. The MR was graduated at first semi-quantitatively and then quantitatively using color flow imaging and the Doppler quantitative method such as regurgitant fraction (RF) according to the American Society of Echocardiography criteria [10]. The MR was defined as mild (mitral RF <30%), moderate (mitral RF; 30–49%), and severe (mitral RF ≥50%). Only moderate and severe MR patients were enrolled to our study. MR patients with SR ($n = 58$) were divided into two groups; primary MR group [MR due to change of mitral valve itself such as prolapse ($n = 21$) and flail leaflet ($n = 6$)] and secondary MR group [MR due to the tethering of the mitral valve leaflet because of LV remodeling such as LV dilation due to ischemia ($n = 25$) and dilated cardiomyopathy ($n = 6$)]. The present study was approved by the ethics committee of our institution and all patients gave written informed consent before participation. The reliability of STE method for the quantification of phasic LAV and LA function has been well established in our previous studies [8,11].

Echocardiography

Echocardiographic studies were performed using a commercially available ultrasound system (iE33, Philips Medical Systems, Best, The Netherlands) that was equipped with a broadband (1–5 MHz) S5-1 probe. All echocardiographic measurements were made according to criteria of the American Society of Echocardiography [12] and were averaged from three heartbeats in MR patients with SR and averaged from five heartbeats in MR patients with AF.

Just before catheterization, LV ejection fraction, LV mass, LA dimension (LAD), and E/e' were measured. LV ejection fraction was measured by bi-plane modified Simpson's method. LV mass was calculated at end diastole using the two-dimensional area-length method: LV mass = $0.8 \times 1.04 \times [(\text{LV dimension} + \text{LV posterior wall thickness} + \text{LV septal wall thickness})^3 - \text{LV dimension}^3] + 0.6g$. Volume and mass were indexed for body surface area. Doppler measurements of mitral inflow E-wave and A-wave velocity were obtained from the apical four-chamber view and tissue Doppler measurement of mitral e' wave velocity was made at the septal mitral annulus.

Speckle tracking analysis

After measurements of the standard echocardiographic parameters, three cardiac cycles were recorded in an apical four-chamber view using gray-scale acquisition to obtain a time–LA strain curve and a time–LAV curve by STE in MR with SR and five cardiac cycles were recorded in MR with AF. To optimize STE, images were obtained at a frame rate of 70–100 frames/s. The off-line time–longitudinal LA strain data analysis and time–LAV curve analysis were performed with QLAB 9.0 software (Philips Medical Systems, Andover, MA, USA) to evaluate LA strain and phasic LAV and LA emptying function (EF). To assess LA strain, LAV and EF, the focus was set at the level of LA and three tracking points were manually placed on an end-diastolic frame on LA endocardial layer (two points at medial and lateral mitral annulus and one point at apex of LA in Fig. 1). The LA was then automatically traced during one cardiac cycle, for regions of interest with a thickness of 3 mm between endocardial and epicardial layer (Fig. 1). The user can optimize both contours globally or regionally. Once completed, the user verifies the tracking based on how well it follows the endocardial and epicardial contours of the left atrium. Maximum, pre-atrial contraction and minimum LAV, and active and total LAEF were measured in sinus rhythm. Active LAEF that reflects LA pump function was defined as (pre-atrial contraction LAV – minimum LAV)/pre-atrial contraction LAV. Total LAEF that reflects LA reservoir function was defined as (maximum LAV – minimum LAV)/maximum LAV as we previously described [8,11]. The ePCWP was calculated as $10.8 - 12.4 \times$ KT index. KT index was defined as $\log_{10}$(active LAEF/minimum LAV index) as we reported [8]. In MR patients with AF, total LAEF was substituted for active LAEF because pre-atrial LAV was not present [8].

Invasive measurements of pulmonary capillary wedge pressure

Mean PCWP was measured with a pulmonary artery balloon-occlusion catheter, and the wedge portion was verified fluoroscopically and by changes in the pressure waveform. Fluid-filled transducers were balanced before the study with zero obtained at the mid-axillary line. The pressure measurements were performed

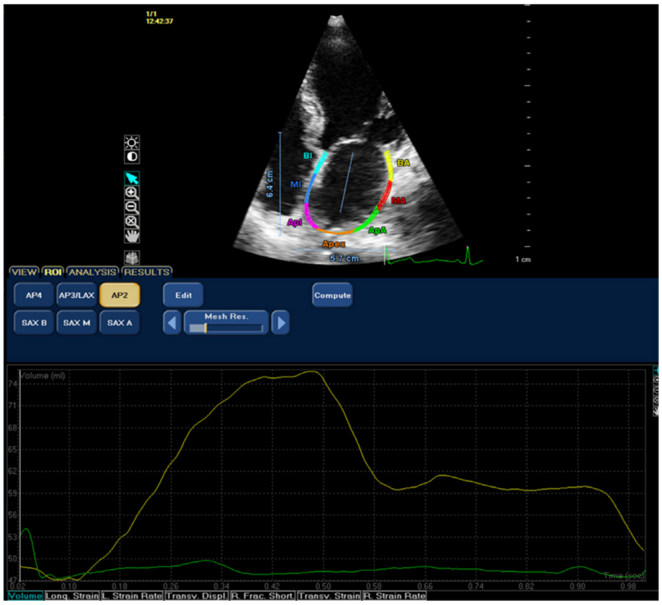

Fig. 1. Representative image of time–left atrial volume curve constructed from speckle tracking echocardiography.
Upper panel shows speckle tracking echocardiography of the left atrium in apical four-chamber view with a thickness of a region of interest of 3 mm. Lower panel shows time–left atrial volume curve constructed from speckle tracking echocardiography (yellow line) by modified Simpson's rule and electrocardiogram (green line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

by investigators who were blinded to the echocardiographic data. Measurements of mean PCWP were made at end-expiration and the average of five cardiac cycles was used as the LV filling pressure.

Statistical analysis

Data are shown as mean ± SD. Differences among groups for the categorical variables were assessed by the χ^2 test or Fisher's exact test. Differences of clinical data among controls, MR patients with SR, and MR patients with AF were analyzed by analysis of variance followed by a Tukey's test for post hoc comparisons. Comparison of clinical data and echocardiographic parameters between controls and MR patients with SR was performed by an unpaired *t*-test. Pearson's correlation coefficients were calculated to assess the relationships between echocardiographic parameters and PCWP measured by catheterization. In MR patients with SR, sensitivity and specificity were calculated using standard definitions, receiver operation characteristic curves were constructed, and the area under the curve was calculated for the prediction of elevated PCWP >15 mmHg, the agreement between different methods to measure PCWP by catheterization and to estimate ePCWP by KT index was assessed with the method of Bland–Altman, and multivariate regression analysis was performed to determine the independent predictors of PCWP. A *p*-value <0.05 was considered statistically significant. Statistical analyses were performed using Stat View version 5.0 (SAS Institute Inc., Cary, NC, USA).

Table 1b
The general characteristics of the primary and secondary MR patients with sinus rhythm.

	Primary MR (n = 27)	Secondary MR (n = 31)	*p*-Value
Age (years)	65 ± 6	69 ± 10	0.05
Male (%)	18 (67)	16 (52)	0.25
Body surface area (m^2)	1.66 ± 0.20	1.61 ± 0.18	0.27
Systolic blood pressure (mmHg)	127 ± 11	130 ± 14	0.28
Diastolic blood pressure (mmHg)	74 ± 5	76 ± 10	0.31
Current smoking (%)	4 (15)	7 (14)	0.25
Diabetes mellitus (%)	6 (22)	9 (29)	0.56
Dyslipidemia (%)	4 (15)	8 (26)	0.30
ARB or ACEI (%)	6 (22)	21 (68)	<0.01
Beta-blocker (%)	3 (11)	14 (45)	<0.01
Calcium channel blocker (%)	5 (19)	13 (42)	0.06
Diuretics (%)	15 (56)	18 (58)	0.85

MR, mitral regurgitation; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor.

Results

The general characteristics of the study population are listed in Tables 1a and 1b. Echocardiographic parameters of controls and MR patients with SR are presented in Table 2. LA assessment by STE was well performed in all subjects owing to the improvement in technology of STE. There was a significant difference in LV ejection fraction between controls and MR patients with SR. The E/e' of MR patients with SR was significantly higher than in controls. Phasic LAVs of MR patients with SR were significantly increased and LA phasic functions of those patients were significantly reduced compared with controls. The ePCWP was significantly higher and LA longitudinal peak strain was lower in MR patients with SR compared with controls.

Analysis on echocardiographic predictor for PCWP in MR patients with SR

The correlation between PCWP and echo parameters in MR patients with SR is shown in Table 3 and Fig. 2. Significant correlation was found between PCWP and LA dimension (r = 0.32, $p < 0.05$) or E/e' (r = 0.31, $p < 0.05$) and also between PCWP and minimum LAV index (r = 0.55, $p < 0.01$) or active LAEF (r = –0.61,

Table 1a
The characteristics of the controls and patients with MR.

	Controls (n = 26)	MR with SR (n = 58)	MR with AF (n = 24)	*p*-Value
Age (years)	67 ± 11	67 ± 8	69 ± 11	0.61
Male (%)	19 (73)	34 (59)	16 (67)	0.42
Body surface area (m^2)	1.66 ± 0.18	1.63 ± 0.19	1.65 ± 0.19	0.83
Systolic blood pressure (mmHg)	127 ± 8	129 ± 13	127 ± 12	0.83
Diastolic blood pressure (mmHg)	77 ± 8	75 ± 8	74 ± 11	0.66
Current smoking (%)	4 (15)	7 (14)	6 (25)	<0.01
Diabetes mellitus (%)	0 (0)	15 (26)	8 (33)	<0.01
Dyslipidemia (%)	0 (0)	12 (21)	6 (25)	0.03

MR, mitral regurgitation; SR, sinus rhythm; AF, atrial fibrillation.

Table 2
Echocardiographic parameters of controls and the patients with MR and sinus rhythm.

	Controls (n = 26)	MR with SR (n = 58)	p-Value
LV mass (g/m^2)	100 ± 12	131 ± 37	<0.001
LV ejection fraction (%)	63 ± 6	55 ± 13	<0.001
Mitral E velocity (cm/s)	78 ± 24	106 ± 36	0.001
Mitral A velocity (cm/s)	92 ± 39	84 ± 29	0.331
Mitral E/A ratio	0.96 ± 0.47	1.54 ± 1.11	0.001
E/e' ratio	10.5 ± 3.3	18.2 ± 8.2	<0.001
LA dimension (mm)	35 ± 5	48 ± 9	<0.001
Maximum LAVI (ml/m^2)	39 ± 9	87 ± 33	<0.001
Minimum LAVI (ml/m^2)	19 ± 6	60 ± 31	<0.001
Total LAEF (%)	52 ± 8	33 ± 12	<0.001
Active LAEF (%)	38 ± 8	19 ± 9	<0.001
LA peak strain (%)	34 ± 12	17 ± 9	<0.001
ePCWP (mmHg)	7.7 ± 2.7	16.6 ± 4.9	<0.001
PCWP (mmHg)		18.2 ± 7.0	

MR, mitral regurgitation; SR, sinus rhythm; LV, left ventricle; E, early filling; A, atrial contraction; E/A, the ratio of early filling velocity to atrial contraction velocity; E/e', the ratio of mitral early filling velocity to mitral annular early diastolic tissue velocity; LA, left atrium; LAVI, left atrial volume index; LAEF, left atrial emptying function; ePCWP, estimated pulmonary capillary wedge pressure by KT index; PCWP, pulmonary capillary wedge pressure.

$p < 0.01$) or total LAEF ($r = -0.51$, $p < 0.01$) or LA strain ($r = -0.50$, $p < 0.01$). The better correlation was found between PCWP and KT index ($r = 0.68$, $p < 0.01$) and between PCWP and ePCWP estimated by KT index ($r = 0.67$, $p < 0.01$). There was also a good correlation between PCWP and ePCWP in both primary and secondary MR ($r = 0.70$ and $r = 0.67$, $p < 0.01$, respectively). Multiple regression analysis including E/e', maximum LAV index, total LAEF, LA strain, and ePCWP revealed that ePCWP estimated by the KT index was an independent predictor of PCWP in MR patients with SR. However, the minimum LAV index, active LAEF, LA dimension, and e' could not be included in the multiple regression analysis due to multicollinearity.

The ePCWP demonstrated good diagnostic accuracy (area under the curve of 0.86), a sensitivity (81%), specificity (71%), positive predictive value (83%), and negative predictive value (68%) to predict elevated PCWP >15 mmHg using a cut-off value of 16 mmHg from the receiver operating characteristic curve (Fig. 3). Bland–Altman analysis confirmed the agreement between PCWP and ePCWP (mean bias 1.6 ± 5.2 mmHg) (Fig. 4).

Additional analysis in MR patients with AF

In additional analysis on relationship between PCWP measured by right heart catheterization and the ePCWP estimated by KT index or E/e' in MR patients with AF, a weak but significant correlation between PCWP and the ePCWP was found ($r = 0.58$, $p = 0.003$), whereas there was no significant correlation between PCWP and E/e' ($r = 0.38$, $p = 0.07$).

Discussion

In this study, we demonstrated for the first time that the ePCWP estimated by KT index is more useful and reliable predictor of PCWP in moderate to severe MR patients with SR including both primary and secondary MR than any other echocardiographic parameters including E/e', LAV, LA function, and LA strain. We also found that the ePCWP by KT index had a weak but significant correlation with PCWP even in MR patients with AF. Furthermore, we demonstrated that not only an increase in LAV but also a reduction in both LA function and LA deformation property such as LA strain assessed by 2D-STE were observed in moderate to severe MR patients with SR compared with those of the controls.

The LA pressure–volume relationship consists of two loops arranged in a horizontal figure-of-eight pattern that incorporates both the active (A loop) and passive (V loop) components of LA function (Fig. 5) [8]. Dernellis et al. reported that there was a linear correlation between minimum LAV index and LA pressure in subjects with normal atrial function, patients with acute myocardial infarction, and patients with chronic heart failure (Fig. 5) [13]. As LV diastolic function continues to decrease, LAV continues to increase [14]. Furthermore, as LV diastolic dysfunction progresses, active LAEF is gradually impaired due to elevated LV stiffness and LV filling pressure, and active LAEF begins to decrease. Thus, as LV end-diastolic pressure increases, LAV increases and active LAEF begins to decrease, indicating that increased LAV and decreased active LAEF reflects the elevated LV end-diastolic pressure. Moreover, Hsiao et al. previously reported the logarithmic correlation between LV filling pressure and LA distensibility [(maximum LAV index − minimum LAV index)/minimum LAV index] that is similar to the total LAEF [(maximum LAV index − minimum LAV index)/maximum LAV index] [14]. Therefore, in our previous study, we determined the logarithmic correlation between PCWP and echo parameters and found that ePCWP assessed by KT index (log active LAEF/minimum LAV index) is a powerful and useful predictor of PCWP [8].

In moderate to severe MR patients with SR, PCWP obtained by the KT index had a significant but moderate correlation with PCWP obtained by right heart catheterization. The physiological changes in the LA in those patients are characterized by increases in LA size and pressure. In MR patients, LAV and LA pressure are more increased at the end systole because of regurgitation and LV early filling. E-wave velocity or e' may be enhanced by increased LAV and LA pressure at early diastole and active LAEF may be also increased according to Frank–Starling law of LA due to volume overload at the end diastole in early stage of MR. However, when LAV and LA

Table 3
The correlation between PCWP and echo parameters in total patients with MR and sinus rhythm, primary MR and secondary MR patients.

	MR with SR (n = 58)	Primary MR (n = 27)	Secondary MR (n = 31)
Mean PCWP (mmHg)	18.2 ± 7.0	18.4 ± 7.2	18.1 ± 6.9
LA dimension	$r = 0.32$, $p = 0.015$	$r = 0.41$, $p = 0.032$	$r = 0.25$, $p = 0.177$
E/e' ratio	$r = 0.31$, $p = 0.015$	$r = 0.25$, $p = 0.203$	$r = 0.38$, $p = 0.036$
Minimum LAVI	$r = 0.55$, $p < 0.001$	$r = 0.66$, $p < 0.001$	$r = 0.47$, $p = 0.007$
Maximum LAVI	$r = 0.51$, $p < 0.001$	$r = 0.59$, $p = 0.002$	$r = 0.46$, $p = 0.010$
Total LAEF	$r = -0.51$, $p < 0.001$	$r = -0.63$, $p = 0.001$	$r = 0.40$, $p = 0.026$
Active LAEF	$r = -0.61$, $p < 0.001$	$r = -0.59$, $p = 0.002$	$r = -0.65$, $p < 0.001$
LA peak strain	$r = -0.50$, $p < 0.001$	$r = -0.55$, $p = 0.002$	$r = -0.47$, $p = 0.008$
KT index	$r = -0.68$, $p < 0.001$	$r = -0.71$, $p < 0.001$	$r = -0.66$, $p < 0.001$
ePCWP by KT index	$r = 0.67$, $p < 0.001$	$r = 0.70$, $p < 0.001$	$r = 0.67$, $p < 0.001$

MR, mitral regurgitation; SR, sinus rhythm; PCWP, pulmonary capillary wedge pressure; LA, left atrium; E/e', the ratio of mitral early filling velocity to mitral annular early diastolic tissue velocity; LAVI, left atrial volume index; EF, emptying function; ePCWP, estimated pulmonary capillary wedge pressure by KT index.

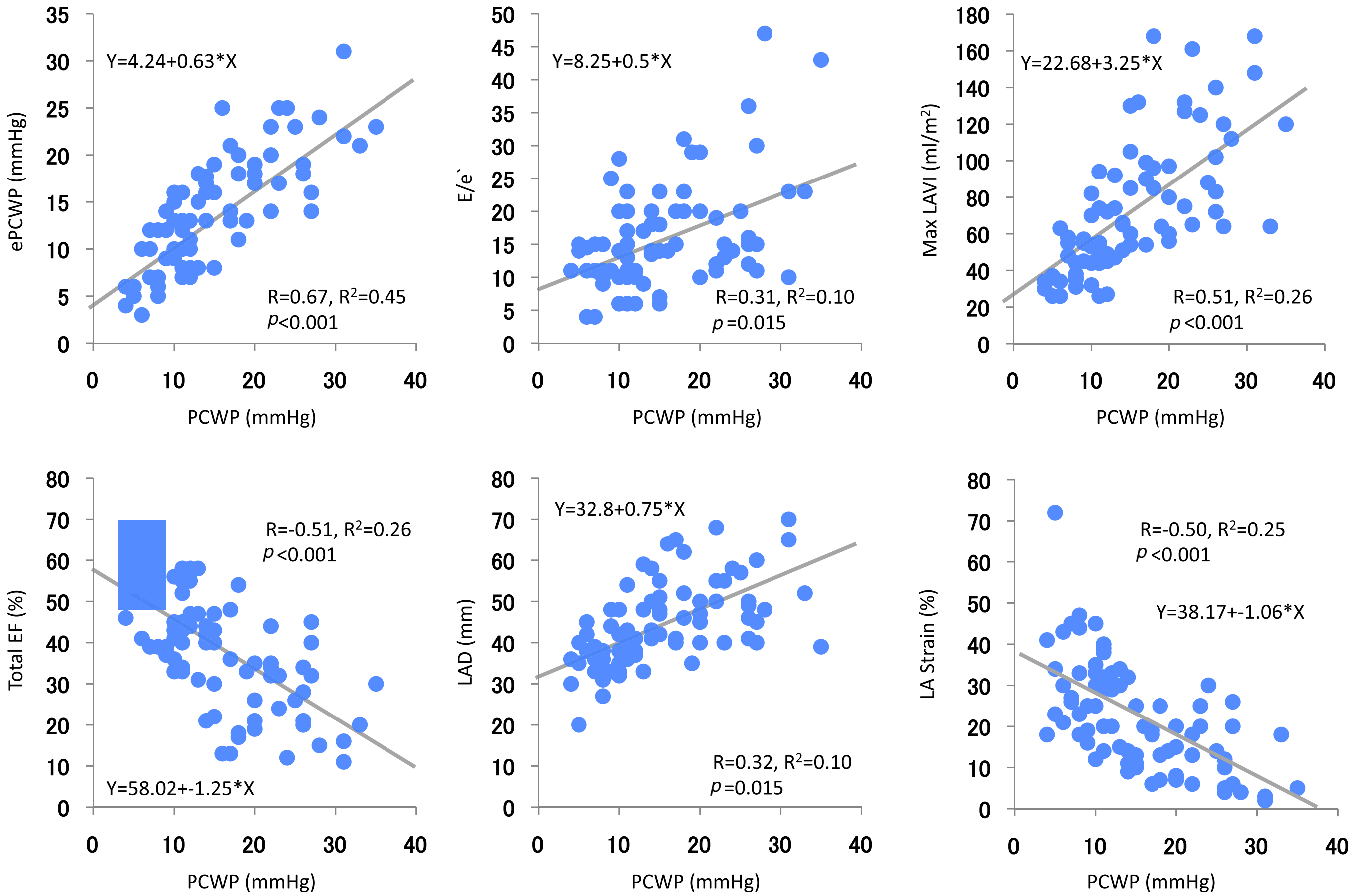

Fig. 2. Correlation between PCWP measured by catheterization and echocardiographic parameters in patients with MR and sinus rhythm.
Relationship between PCWP measured by right heart catheterization and PCWP estimated by the KT index, *E*/*e*′, maximum LAV index, total LAEF, LAD, and LA peak strain in patients with mitral regurgitation and sinus rhythm. The relationships were evaluated by simple linear regression analysis. PCWP, pulmonary capillary wedge pressure; MR, mitral regurgitation; ePCWP, estimated pulmonary capillary wedge pressure by KT index; *E*/*e*′, the ratio of early diastolic inflow velocity to mitral annular tissue velocity; Max LAVI, maximum left atrial volume index; Total LAEF, total left atrial emptying function; LAD, left atrial dimension.

pressure overload continues to exist in MR, active LAEF may begin to decrease in proportion to increased LA pressure as minimum LAV at end diastole increases due to LA structural and functional remodeling. Therefore, it is reasonable to think that the combined assessment of minimum LAV after LA contraction and active LAEF may reflect PCWP even in MR. Thus, we sought to assess the usefulness of KT index to predict PCWP in MR, because the ePCWP by KT index was calculated by the combination of active LAEF and minimum LAV index measured at end diastole. However, the magnitude of changes in LAV and LA pressure chiefly depends on the rapidity and severity of MR [15] and the peak of the V wave of LA pressure is delayed in MR and the V wave in acute MR is especially elevated. This may be the reason why the relationship between PCWP obtained by the KT index and right heart catheterization was not strong.

The LA and LV in chronic MR are subject to increased volume overload, and increased LA mechanical work in chronic MR may contribute to LA remodeling and LA failure [16]. Although the assessment of LA size provides prognostic information and has been routinely performed with transthoracic echocardiography, information on LA function could provide more important insight [11] and be helpful in the management of MR patients. In patients with heart failure, increased LVFP is the primary mechanism responsible for dyspnea. Thus, the assessment of LV diastolic function including LVFP or PCWP is of exceeding importance in terms of diagnosis, therapy, and follow-up of heart failure caused by MR.

The echocardiographic estimation of LVFP may be influenced by the degree of MR. In many previous studies about *E*/*e*′ performed by Nagueh et al. or Ommen et al., MR patients were excluded [4,17]. Some previous studies have reported on the estimation of PCWP by using mitral inflow in MR patients [1,5,18]. However, among several measurements using mitral inflow including E/A ratio, deceleration time, and isovolumic relaxation time to predict PCWP [19], the best correlations between Doppler measurements and PCWP were observed in patients without significant MR [17].

Furthermore, there are conflicting results about the use of *E*/*e*′ in the estimation of LVFP in MR patients. Bruch et al. reported that *E*/*e*′ correlated significantly with LVEDP in patients with secondary MR [5]. Moreover, Van de Veire et al. showed that *E*/*e*′ was independently predicted by ischemic (secondary) MR severity [20]. On the other hand, Yesildag et al. did not show that *E*/*e*′ had any association with LVEDP in patients with secondary MR [1]. Agricola et al. showed that *E*/*e*′ was an independent predictor of LVEDP in primary MR [21]. There has not yet been an elucidated echocardiographic parameter to predict PCWP in MR patients.

STE is a novel technique that allows for a non-invasive assessment of atrial function with the advantage of being angle-independent and to be less affected by reverberations, side lobes and drop out artifacts [8]. STE provides information on not only time–LAV curve and phasic LA function but also LA deformation property such as LA peak longitudinal strain. LA strain is a parameter to permit the quantification of LA [9] and a proposed alternative approach for an LV filling pressure estimation [22]. It

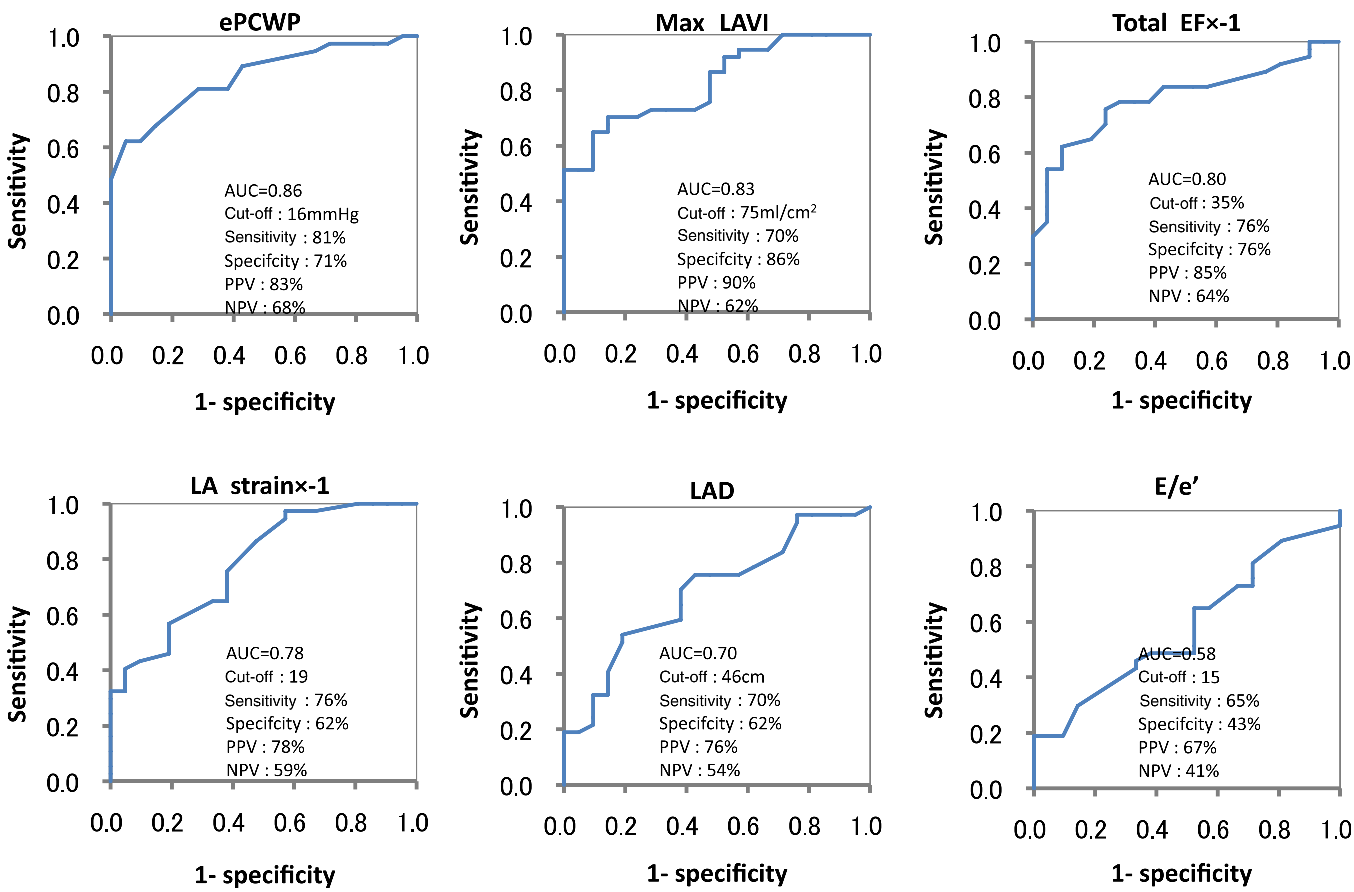

Fig. 3. Receiver operating characteristic curves of the echocardiographic parameters for prediction of PCWP >15 mmHg in patients with MR and sinus rhythm. Receiver operating characteristic curves of the ePCWP, *E*/*e*′, maximum LAV index, total LAEF, LAD, and LA peak strain for predicting an elevated PCWP (>15 mmHg) in patients with MR and sinus rhythm. MR, mitral regurgitation; ePCWP, pulmonary capillary wedge pressure estimated by the KT index; *E*/*e*′, the ratio of early diastolic inflow velocity to mitral annular tissue velocity; Max LAVI, maximum left atrial volume index; Total LAEF, total left atrial emptying function; LAD, left atrial dimension.

was reported that LA longitudinal deformation is higher in mild MR patients but that it appears depressed in moderate and severe MR patients compared with the controls without MR [9], which is concomitant with our finding. We examined the various echocardiographic parameters including *E*/*e*′, LA size, LA function, and novel indices such as ePCWP and LA strain using STE to elucidate the most reliable predictor of PCWP in moderate to severe MR patients with SR including both primary and secondary MR. We found that the ePCWP estimated by the combination of LA function and volume using 2D-STE (KT index) is the best predictor of PCWP

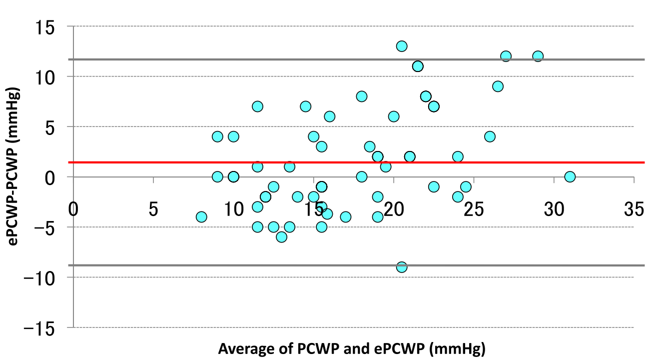

Fig. 4. Bland–Altman analysis. Bland–Altman agreement plot comparing PCWP and ePCWP.
Bland–Altman analysis is shown to compare PCWP measured by right heart catheterization and PCWP estimated by the KT index. The middle red line shows the average difference between the methods, and the upper and lower lines show the limits of agreement (±1.96 × SD of the difference). PCWP, pulmonary capillary wedge pressure; ePCWP, estimated pulmonary capillary wedge pressure by KT index. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of the article.)

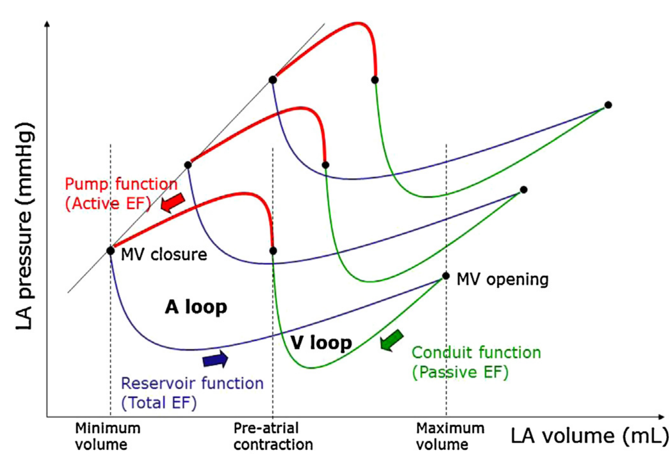

Fig. 5. Left atrial pressure–volume relationship.
Left atrial pressure–volume relationship consists of the active loop (A) and passive loop (V) in normal subjects (left and bottom loop), acute myocardial infarction (mid loop) and chronic heart failure (right and upper loop). Note the linear correlation between minimum LAV and LA pressure in three subjects. LA, left atrium; MV, mitral valve; EF, emptying function.

measured by cardiac catheterization among echocardiographic parameters in MR patients with SR.

We reported that intriguingly, the ePCWP obtained by the KT index in patients with AF had a good agreement with PCWP obtained by right heart catheterization even using the same regression equation as the patients with SR [8]. We also reported that the reason can be speculated that the ratio of maximum LAV index to minimum LAV index (1.21) in the patients with AF was similar to the ratio of pre-atrial contraction LAV index to minimum LAV index (1.19) in the patients with SR [8]. In the present study, the ratio of maximum LAV index to minimum LAV index (1.29) in MR patients with AF is also similar to the ratio of pre-atrial contraction LAV index to minimum LAV index (1.21) in MR patients with SR. We examined additional moderate to severe MR patients with AF, and found that the ePCWP estimated by KT index in those patients had a weak but significant correlation with PCWP measured by right heart catheterization.

Study limitations

There were several limitations in the present study. First, we evaluated only a small number of MR patients. We found the significant correlation between ePCWP and PCWP in such a small number of MR patients but the value of correlation co-efficiency was not so high. Second, the accurate duration of the history of MR was unknown in some patients and the study population of moderate to severe MR included both acute MR such as MR due to tendon rupture and chronic MR. The study population should be divided according to the duration of MR. Third, we assessed LA volume, function, and strain only in apical four-chamber view, because there were a lot of poor recordings in apical two-chamber view as we reported [8]. Evaluation of ePCWP estimated by the combination of LA function and LAV from both apical four- and two-chamber view in a large number of MR patients will be required in a future study. Finally, there are the other echocardiographic parameters to noninvasively estimate LV filling pressure such as the ratio of isovolumetric relaxation time to the interval between the onset of mitral E wave velocity and annular early diastolic tissue velocity by tissue Doppler or the difference between mitral regurgitant pressure gradient estimated by the modified Bernoulli equation and systolic blood pressure. However, we did not examine these noninvasive echo parameters to estimate LV filling pressure in the present study. Therefore, current results and conclusions require additional validation in a larger population including these noninvasive echocardiographic estimates of PCWP.

Conclusion

The ePCWP estimated by the KT index ($\log_{10}$ active LAEF/minimum LAV index) was a useful and reliable echocardiographic parameter to predict PCWP in moderate to severe MR patients with SR including both primary and secondary MR and might be also useful in MR patients with AF. The ePCWP may have an incremental value in the clinical setting to decide therapeutic strategy in MR due to the increase in heart failure with MR.

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Conflict of interest

None of the authors have a conflict of interest with this manuscript.

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